A 3D-MODEL FOR COMPUTER SIMULATION OF ATRIAL ELECTROPHYSIOLOGY

Magnus Fredby , Håkan Elmqvist
Division of medical engineering, Department of Medical laboraroty sciences and engineering,
Karolinska Institutet, Stockholm, Sweden

Abstract- **The presented implementation is a three-dimensional isotropic monodomain reaction-diffusion model with a realistic geometry coupled with the atrial ion model proposed by Nygren *et al.* The partial differential equations are solved by a Garlekin finite element method in space and a forward Euler approximation in time. Simulations yields the expected results and the computational performance of the model is good considering the size of the problem.**
Keywords - Simulation, electrophysiology, atrial, cardiac

I. INTRODUCTION

A fine granularity computer model would be useful to further elucidate mechanisms behind atrial arrhythmia. This kind of information is hard, if not impossible, to extract from animal models and *in vitro* experiments. Knowing the involved ionic currents, new pharmaceuticals acting on the responsible channels might be developed. The possibility of simulating activation patterns may be useful in determining the electrophysiological effect of surgical procedures. Maybe pacing strategies can be developed that restore the atrial rhythm.

Two approaches towards simulation of the cardiac electrical activity constitute the mainstream of proposed models; cellular automata models and reaction-diffusion models [1,2]. Reaction-diffusion models assume that the pseudo-syncytical structure of the cardiac tissue can be regarded as a single volume and uses a diffusion equation to model passive spread of the action potential and an ion current model represents the active phase (the "reaction").

The existing ion models of cardiac myocytes are quite complex. There are several ionic currents and cellular subspaces involved in the formation of action potentials and the recovery afterwards.

Simulation using reaction-diffusion models require numerical methods. Traditionally finite difference methods have been applied. However, Rogers and McCulloch have presented a hybrid finite element method [3].

II. METHODOLOGY

The implemented model is an isotropic monodomain reaction-diffusion model[2,4] with von Neumann boundary conditions coupled with the membrane current model of Nygren *et al* [5]. The equation to be solved is thus

$$\nabla\cdot(\mathbf{D}\nabla V)=\beta\left(C_m\frac{dV}{dt}+I_{ion}\right)-I_{sm} \qquad (1)$$

$\mathbf{D}\nabla V\cdot\mathbf{n}=0$ at boundary

where V is the transmembrane voltage, I_{ion} the total sarcolemmal ion current calculated from the Nygren model and I_{sm} stimulation pulses. **D** is the conductivity tensor, C_m the transmembrane capacitivity and β the cell surface area to volume ratio. **n** is a vector orthogonal to the boundary.

The conductivity tensor, **D**, is in the anisotropic case a second rank tensor but reduces to an invariant in an isotropic model.

A. Solution method

To generate the element matrices we will apply the Garlekin finite element method to the reaction-diffusion equation.

The domain (the myocardium) is subdivided into a set of finite cubic elements with nodes located at the vertices. In this paper we use a Cartesian global coordinate system and element coordinate systems aligned with the global system (Fig 1).

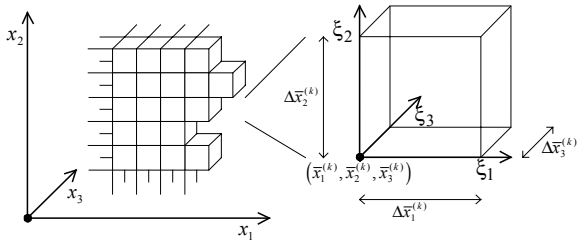

Fig. 1. Definition of the local coordinate system for element *k*.

The value of V, I_{ion} and I_{sm} within the elements is interpolated from the value of the corresponding variable at the nodes. A set of linear Lagrangian interpolation functions are defined in the element coordinate system:

$$\begin{aligned}
\psi_0&=\varphi_0(\xi_1)\varphi_0(\xi_2)\varphi_0(\xi_3) & \psi_4&=\varphi_0(\xi_1)\varphi_0(\xi_2)\varphi_1(\xi_3)\\
\psi_1&=\varphi_1(\xi_1)\varphi_0(\xi_2)\varphi_0(\xi_3) & \psi_5&=\varphi_1(\xi_1)\varphi_0(\xi_2)\varphi_1(\xi_3)\\
\psi_2&=\varphi_0(\xi_1)\varphi_1(\xi_2)\varphi_0(\xi_3) & \psi_6&=\varphi_0(\xi_1)\varphi_1(\xi_2)\varphi_1(\xi_3)\\
\psi_3&=\varphi_1(\xi_1)\varphi_1(\xi_2)\varphi_0(\xi_3) & \psi_7&=\varphi_1(\xi_1)\varphi_1(\xi_2)\varphi_1(\xi_3)
\end{aligned}$$

where

$$\varphi_0(\xi)=\begin{cases}1-\xi & 0\le\xi\le1\\ 0 & \xi<0,\xi>1\end{cases}$$
$$\varphi_1(\xi)=\begin{cases}\xi & 0\le\xi\le1\\ 0 & \xi<0,\xi>1\end{cases} \qquad (1)$$

To approximate V we use a weighted residual formulation [6] of the reaction diffusion equation, here written in tensor notation (summation convention applies), with the interpolation functions as weighting functions. We will also apply the product rule of derivatives followed by the divergence theorem to the left-hand side, the surface integral term will then vanish due to boundary conditions. Finally, we rearrange the equations and move nodal parameters (since they are independent of space coordinates)

Report Documentation Page

Report Date	Report Type	Dates Covered (from... to)
25OCT2001	N/A	-

Title and Subtitle A 3D-Model for Computer Simulation of Atrial Electrophysiology	**Contract Number**
	Grant Number
	Program Element Number
Author(s)	**Project Number**
	Task Number
	Work Unit Number
Performing Organization Name(s) and Address(es) Division of medical engineering, Department of Medical laboraroty sciences and engineering, Karolinska Institutet, Stockholm, Sweden	**Performing Organization Report Number**
Sponsoring/Monitoring Agency Name(s) and Address(es) US Army Research, Development & Standardization Group (UK) PSC 802 Box 15 FPO AE 09499-1500	**Sponsor/Monitor's Acronym(s)**
	Sponsor/Monitor's Report Number(s)

Distribution/Availability Statement
Approved for public release, distribution unlimited

Supplementary Notes
Papers from the 23rd Annual International Conference of the IEEE ENgineering in Medicine and Biology Society, October 25-28, 2001, held in Istanbul, Turkey. See also ADM001351 for entire conference on cd-rom., The original document contains color images.

Abstract

Subject Terms

Report Classification unclassified	**Classification of this page** unclassified
Classification of Abstract unclassified	**Limitation of Abstract** UU

Number of Pages
4

and β and C_m (they are assumed to be constant over the entire domain) out of the integral:

$$\frac{dV^i}{dt}\sum_{k=1}^{M}\int_0^1\int_0^1\int_0^1 \Gamma_i^{a(k)}\psi_a\Gamma_j^{b(k)}\psi_b\, d\xi_1 d\xi_2 d\xi_3 =$$

$$V^i\frac{-1}{\beta C_m}\sum_{k=1}^{M}\int_0^1\int_0^1\int_0^1 D^{qp}\Gamma_i^{a(k)}\psi_{a,r}\frac{\partial\xi_r}{\partial x_q}\Gamma_j^{b(k)}\psi_{b,s}\frac{\partial\xi_s}{\partial x_p}d\xi_1 d\xi_2 d\xi_3 +$$

$$\left(I_{ion}^i-\frac{I_{sm}^i}{\beta}\right)\frac{-1}{C_m}\sum_{k=1}^{M}\int_0^1\int_0^1\int_0^1 \Gamma_i^{a(k)}\psi_a\Gamma_j^{b(k)}\psi_b\, d\xi_1 d\xi_2 d\xi_3$$

where $\Gamma_i^{a(k)}$ denotes a mapping from index a in element k to the global index i. Referring to Fig 1 we note that

$$\frac{\partial\xi_p}{\partial x_q}=\begin{cases}\frac{1}{\Delta\bar{x}_q^{(k)}} & q=p\\ 0 & q\neq p\end{cases}$$

The integrals may be evaluated symbolically and assembled into the global matrices, i.e. map the local node numbers to their corresponding global node numbers and sum the contributions from each element. The result is a system of ordinary differential equations (ODEs):

CV KV TD3K TD33hh

one term of the sum is deduced each iteration. This is more efficient than performing the transposition and the equivalence is easily seen in the formula stated above.

Presentation

The visualizer draws a three-dimensional picture using the mesh. The nodal potentials are then color-mapped to show the potentials at a given time. By selecting a point a graph of the potential variation over time is drawn.

C. Simulation parameters

A voxel image of the human atria was provided by Rok Hren at the University of Utah (courtesy of Milan Horacek)[8]. The final mesh consists of 58235 nodes and 40681 elements.

In the presented simulations the ion model was left unaltered, leaving only the capacitivity C_m, the conductivity D and the area to volume ratio β to be assigned. In this application, due to the fact that the model is isotropic, D is a scalar.

Nygren *et al.* define C_m for the *whole* cell to be 0.050 nF and I_{ion} is defined as *total* current passing into the cell; no values regarding the assumed area are presented. They do, however, assume an intracellular volume (Vol_i) of 0.005884 nL. Using these values we may easily calculate all the necessary parameters except D. Since the presented values for the intracellular conductivity varies considerably in the literature we have chosen to adjust D to give a reasonable conduction velocity; to simulate normal activation D was set to 2.0 mS/mm. This is within the range of presented values.

Stimulation pulses with an amplitude of 1.5 nA and a duration of 6 ms was added to the ion currents of the nodes of two surfaces (i.e. to eight nodes) close to each other to invoke action potentials.

III. Results

A. Computational performance and memory requirements

The routine of primary interest, the one that calculates the ion currents and repeatedly solves the equation system, requires about 12 hours to simulate 1 second of atrial activity.

The voxel image file and the mesh file require 2 and 3 MB, respectively. The assembled matrices contains 1.5 million entries each and the factorized 8.5 million entries. The storage required by these matrices adds up to 130 MB. The state file contains the potential and the 28 ion model state variables at the each node; this requires 13 MB.

The size of the simulation file (i.e. the node potentials at selected times) varies due to the run-length encoding scheme; as a rule of thumb, 200 MB per simulated second.

B. Simulation results

Fig 3 shows the potential distribution from a "top view" at selected times after a stimulation pulse was applied in the right atrium at point between vena cava inferior and superior. Fig 3 also shows the action potential at a selected point in the model.

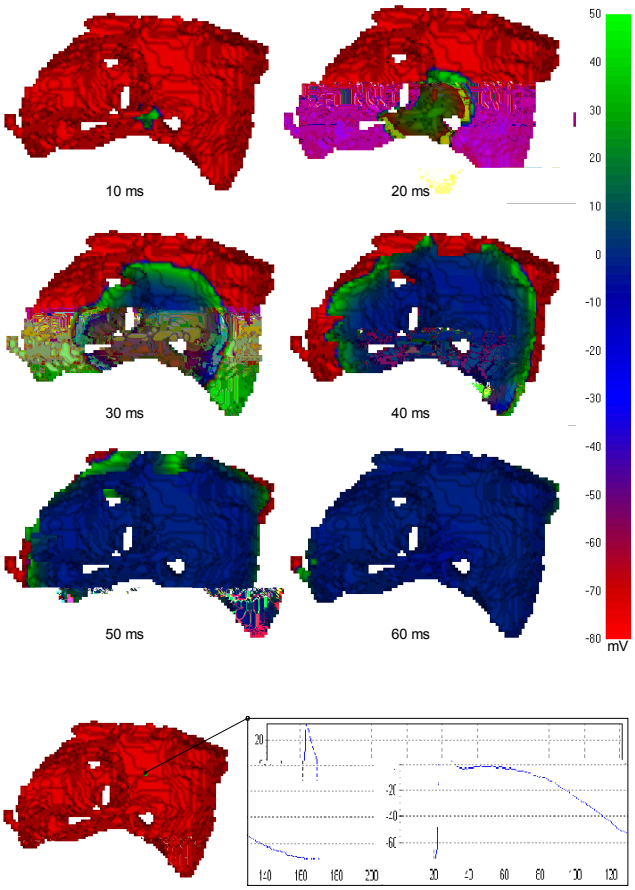

Fig. 3. Activation pattern following stimulation pulse. This figure also shows an action potential at the marked position.

IV. Discussion

A. The model

The implemented ion model is the one proposed by Nygren *et al.* This is the most recent published model of the atrial myocyte and is based mainly on human data. In the future a SA-model will be used for the SA-node. This model incorporates the ion currents and concentrations believed to be most significant. These ion currents and concentrations are altered in ischemic and metabolic conditions and by modifying the magnitude and timing, of these currents and concentrations the model ought to be able to reflect many clinical situations. Hormones and neurotransmitters modifying ion channel characteristica may also be incorporated. Structural properties, such as infarctions, may be incorporated in the mesh or the diffusion tensor. Pharmaceutica usually either acts as neurotransmitter agonists or antagonists or as blockers of specific ion channels. Again, by modifying ion channel properties, the effect of these pharmaceutica may be simulated.

Surgical procedures, such as maze operations and catether ablations, modifies the (electrical) structure of the atria by introducing scars or infarctions. These structural changes may be reflected as changes in the diffusion tensor.

Electrical therapies may be modeled by introducing stimulation pulses at selected points in the model. Input from sensing electrodes is available since the potential distribution is known. Pacing algorithms are easily interfaced to existing code.

Due to lack of data, the implemented model is isotropic. Though, extending it to an ansisotropic model would only require an estimate of the diffusion tensor and the addition of a quadrature algorithm

B. Solution method and implementation

Finite element methods may easily handle von Neumann conditions when Garlekin weighting functions are used; the complexity of the problem is actually reduced. The explicit method used to approximate the time derivatives of potentials as well as in the differential equations of the ion model poses a risk of instability. The required time step might be smaller than what would be required by an implicit method, but we believe that the speed of the explicit method most likely outweigh the reduction of time step possible with an implicit method.

The design criteria may summarized as: *accuracy*, *speed*, *extensibility* and *portability*. These apply in variable degree to different steps in the solution process. Accuracy is mostly governed by the choice of solution method and ion model; at the implementation level there are three factors that needs to be considered: floating point precision, order of expression evaluation and the magnitude of the time-step taken during the solution of the ODEs. Speed is a main concern when the equation system is to be solved due to large number of iterations, while longer run-times are acceptable in the preparation of the matrices. Also, if the run-time is rendered unacceptable, emigration to a more powerful platform would be of interest. Thus, portability is of importance.

C. Computational performance and memory requirements

The present computer (Pentium III 800MHz) requires about 2 seconds for each timestep due to the large number of equations, and the expensive exponential operations required by the nonlinear right-hand sides of the ion model. This accumulates to a barely acceptable simulation time of roughly 12 hours for each simulated second.

There are today two steps in the solution process that are outweighing the others; the two triangular solve steps (forward elimination and backward substitution) and the ion model operations. The factorization step generates a triangular matrix containing about 8.5 million entries with the permutation algorithm used today. The current permutation algorithm is balanced between the number of fill-ins generated and the time used to find the permutation considering a system that is supposed to be solved once. This is far from optimal in this application since the triangular solve is iterated fifty thousand times for each simulated second while the permutation is only sought once.

We also plan to develop a parallelized version of the algorithm.

D. Simulation results

Simulations of a single wavefront performed with this model show a reasonable agreement with available mapping studies[9,10] regarding average conduction velocity. The refractory period is also in line with published data. The model behaves as expected when two activation fronts collide.

V. CONCLUSIONS

The presented implementation is an three-dimensional isotropic monodomain reaction-diffusion model with a realistic geometry coupled with the atrial ion model proposed by Nygren *et al.* Thus, it allows conduction velocity and refractory periods to adjusted. Normal anisotropy is not included in the current model due to the absence of data but the modification is rather easy.

The computational performance of the model is good considering the size of the problem. However, run-times needs to further reduced for the model to reach its full potential.

REFERENCES

[1] N.V. Thakor, J.M.J. Ferrero, J. Saiz, B.I. Gramatikov, J.M. Ferrero, ”Electrophysiologic Models of Heart Cells and Cell Networks. Enabling a Better Understanding of Arrhythmias and Heart Disease”. *IEEE Eng. Med. Biol. Mag., vol. 17,* pp. 73-83, Sept-Oct 1998.

[2] C.S. Henriquez, A.A. Papazoglou, ”Using Computer Models to Understand the Roles of Tissue Structure and Membrane Dynamics in Arrhythmogenesis”. *Proc. IEEE*, vol. 84: pp. 334-354, 1996.

[3] J.M. Rogers, A.D. McCulloch, ”A Collocation-Garlekin Finite Element Model of Cardiac Action Potential Propagation”. *IEEE Trans. Biomed. Eng.*, vol. 41, pp. 743-757, Aug 1994.

[4] C.S. Henriquez, ”Simulating the electrical behavior of cardiac tissue using the bidomain model”. *Crit. Rev. Biomed. Eng.,* vol. 21, pp. 1-77, 1993.

[5] A. Nygren, C. Fiset, L. Firek, J.W. Clark, D.S. Lindblad, R.B. Clark, W.R. Giles, ”Mathematical Model of an Adult Human Atrial Cell. the Role of K^+ Currents in Repolarization”. *Circ. Res.*, vol. 82, pp. 63-81, Jan 1998.

[6] W.F. Ames, *Numerical methods for partial differential equations*, 3rd ed., Academic Press Inc., 1992

[7] I.S. Duff, A.M. Erisman, J.K. Reid, *Direct methods for sparse matrices*, Oxford University press, 1997

[8] W.J. Eifler, E. Macchi, H.J.Ritsema van Eck, B.M. Horacek, P.M. Rautaharju, ”Mechanism of generation of body surface electrocardiographic P-waves in normal, middle and lower sinus rhytms”, *Cirk. Res.* vol.48, pp. 168-182, Feb 1981

[9] M.A. Allesie, W.J.E.P. Lammers, P.L. Rensma, F.I.M. Bonke, ”Flutter and Fibrillation in Experimental Models: What Has Been Learned that Can Be Applied to Humans”, in Brugada P, Wellens HJJ (eds) *Cardiac Arrythmias: Where To Go From Here?*, Futura Publishing Company Inc. 1987, pp. 67-82

[10] M. Holm, ”Chronic Atrial Fibrillation in man. Activation, organisation and characterisation” PhD dissertion,, Lund Univ., Sweden 1997